should be accompanied by a statement that the health consequences of the change are unproven (or unknown).

Given that considerable time will be needed to enact appropriate legislation, to staff a new regulatory agency, and to bring whole classes of products into a new regulatory system, a number of modified tobacco products with risk-reduction claims may enter the marketplace in coming years without regulatory review, assuming they are positioned not to fall under the drug or device laws. The committee views this situation with alarm but cannot offer a ready solution. Perhaps tobacco manufacturers would be willing to demonstrate their good faith by agreeing to voluntarily submit claims of reduced exposure or reduced harm to FDA, FTC, CDC, or some other appropriate agency for its review and comment, and to conform to agency suggestions pending legislative action. The committee emphasizes, however, that any purported harm-reducing products that have been put on the market before enactment of regulatory legislation should not be grandfathered or exempted from rigorous scientific and regulatory scrutiny.

relate to overall monitoring

Principle 6: Postmarketing Surveillance

The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct postmarketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims.

The committee has repeatedly emphasized that since definitive information on the ultimate value of a PREP cannot be determined at the time of its initial marketing, the true extent of its long-term benefit (or possible harm) will remain uncertain unless specific surveillance and epidemiological studies are conducted after the product is marketed. The FDA already has the authority to require pharmaceutical manufacturers to conduct such studies for the purpose of monitoring drug-related health risks. The designated regulatory agency for tobacco-related PREPs should have equivalent authority to require manufacturers who seek to make reduced-risk claims to sponsor surveillance and epidemiological studies in appropriate cases. These studies should be designed to assess not only the benefit of the product in reducing the risk of smoking but also the degree to which the product has served to maintain as smokers those who might otherwise have quit and/or to recruit new smokers. The quality of these studies should be high so that the results can permit modification of claims as knowledge evolves.

The committee envisions that a plan or protocol for such a study (or studies) would commonly be required at the time of approval of the claim. Whether a postmarketing study is necessary should be judged by the regulatory agency on a case-by-case basis. The agency can also be expected to take steps to ensure the scientific integrity of such studies by requiring appropriate monitoring and, where necessary, an independent safety monitoring board. In addition to the authority to require manufacturers to sponsor postmarketing studies, the regulatory agency should also have in-house expertise in epidemiology. Such expertise is needed to deal competently with scientists in industry and peers in the field, to operate an adverse event reporting system, and to sponsor selected studies when necessary. As discussed in Chapter 6, the regulatory agency, in collaboration with other public health agencies, should conduct an active program of surveillance for all tobacco products, including conventional ones, modified products that are not accompanied by health claims, and PREPs. It is particularly important for public health authorities to monitor patterns of initiation and progression of use, including the interactions of product use (substitution and supplementation), for all PREPs.

PM3006857036

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

packaging and in advertising. Specifically, the IOM (1994) report made the following recommendations:

> Based on current knowledge, Congress should enact specific warning and format requirements now, and should delegate regulatory responsibility for future modifications to the secretary of health and human services. The secretary should ensure that ongoing research is conducted on the effectiveness of prescribed warnings. Congress lacks the institutional expertise and flexibility to monitor the efficacy of regulatory innovations and to respond to new information. Authority to amend the warnings should be delegated to an appropriate regulatory agency. The secretary should be empowered to modify the format or content of existing warnings and to prescribe additional warnings, whenever such action is reasonably necessary to achieve effective communication of significant information regarding the health consequences of tobacco use or to discourage consumption of tobacco products.

The committee endorses this recommendation. The need to implement this approach is all the more evident now in light of the emerging market for products that purport to reduce the risk of tobacco use.

One of the recurrent questions in the regulation of health claims is when to permit a claim that a product *may* reduce the risk of disease. Such a statement may be misleading even though it is not false. Assuming substantial proof of exposure reduction, what type of evidence must be produced in support of a claim that the product *may*, as a result, reduce the risk of disease? Is inference based solely on the existence of a dose–response relationship sufficient? How strong must the evidence be? What is the significance of counterevidence? How much weight should be given to favorable changes in biomarkers that are biologically rational but not yet proven to be true surrogate end points? Although these are questions that will have to be addressed by the regulatory agency in due course, the committee itself is disinclined to permit claims that the product "may" or "might" reduce the risk of disease (or that "growing evidence suggests that the risk is reduced") unless, as judged by the regulatory agency after review by an independent scientific advisory committee, the degree of exposure reduction is likely to result in a decrease in tobacco-related morbidity or mortality that can be measured in subsequent epidemiological studies.

Another question must then be faced. Assume that the agency finds insufficient evidence under such a demanding standard to support a claim that the exposure-reducing product "may reduce the risk" of a particular disease. Should the manufacturer be permitted to make the statement (which is not false) as along as it is accompanied by a disclaimer to the effect that the regulatory agency has not approved the statement? This approach is receiving increasing attention in other regulatory contexts in light of a few judicial decisions holding that regulatory agencies must allow manufacturers to make the unproven statement, together with a disclaimer, under the First Amendment (Gilhooley, 2000). The committee assumes that the First Amendment does not require such a permissive approach and is inclined to be much more cautious in light of the history of public health mistakes in tobacco product innovation. In the committee's judgment, in the absence of sufficient scientific evidence to support a claim that a product may reduce the risk of disease, any claim of reduced exposure to tobacco toxicants

PM3006857037

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

the other hand, neither is the public health served if smokers are discouraged by unduly cautionary language from using a new product with the potential for real risk reduction. The problem of conveying balance in communicating health benefits and risks is not unique to tobacco-related PREPs, and the large body of experience in other areas of health and safety regulation may be applicable to these products as well.

The agency will have to direct its attention to the language used as well as the labeling format. Some illustrations, based on existing formats, follow:

- Current cigarette labeling contains warnings that smoking causes lung cancer, heart disease, and emphysema and may cause birth defects. If warranted by scientific evidence, such warnings could be accompanied by a statement that the modified product might carry a reduced risk of one or more of these conditions.
- Current food labeling has on each package a table displaying a quantitative analysis of nutritional content. This approach could be applied to selected ingredients and constituents of tobacco products or tobacco smoke, such as known carcinogens and CO.
- Food-labeling tables express nutritional content not only as grams per serving but also as a percentage of average daily intake. One could envision tobacco product labeling with a similar table that shows exposure or yield ranges for particular toxicants or perhaps ranks the levels of exposure or yield as high, average or low. These terms could be specifically defined and would perhaps be less misleading than such terms as "light".
- One could also envision the use of words such as "high", "average", or "low", again carefully defined, in a "risk" column in such a table. Pictograms, such as those that appear in poison control warnings, or icons might be used instead of words. It is essential that such labeling in the end be perceived as denoting degrees of risk, not as signifying or implying safety. The message that cessation is the only safe choice must not be obscured or lost.
- The agency should also consider requiring that labels for PREPs that make exposure reduction claims disclose that the reduction in exposure depends upon the user not compensating for the reduction by increasing use or by inhaling more deeply. Consideration should also be given to a disclosure that the health benefits of the product's exposure reduction have not yet been established in scientifically recognized tests or ongoing studies. Such a disclosure would guard against consumer confusion that risk reduction benefits have been proven. Furthermore, such a disclosure would provide an incentive to manufacturers to do more research on the health effects of exposure reduction. The FTC should consider requiring similar disclosures under its existing authority if new legislation is not adopted.

The committee does not have recommendations on the specific form of labeling that is optimal for tobacco-related PREPs. (The formats cited in the foregoing examples are meant only to be illustrative.) This topic deserves the sustained attention of experts in communication and marketing, with the intent of identifying the optimal approach for conveying in a simple format specific information on exposure reduction, the potential for risk reduction, and the associated uncertainty. This information must be balanced, accurate, informative, and not misleading.

Growing Up Tobacco Free (IOM, 1994) reviewed the history of mandated tobacco health warnings; called attention to the inadequacy of the existing warnings (both in content and format); reviewed recent initiatives in other countries, especially Canada; and recommended a number of legislative measures to increase the salience and effectiveness of health warnings on

PM3006857038

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

permissible, the agency should have the authority to take prompt action against specific advertising or promotional campaigns or practices that are false or misleading. This authority should include the power to require corrective advertising.

The committee considered the alternative of recommending that the advertising and promotion of tobacco-related PREPs be included under the present system of regulation for tobacco products in general. For the reasons noted previously, however, the committee considers this system to be insufficient to the task. In the judgment of the committee, a harm reduction strategy using tobacco-related PREPs cannot be implemented successfully unless consumers are fully informed through accurate labeling and advertising about the health consequences of using all types of tobacco products and about the substantial gaps in scientific knowledge. The committee finds no justification for continuing the current situation in which pharmaceutical products intended to aid smoking cessation—the desired public health goal—must be labeled and promoted truthfully under a "not false or misleading" standard, while tobacco products claiming to reduce exposure or risk—at best a partial and uncertain step toward disease reduction—can be promoted under generic consumer deception laws, with the burden of proof on the FTC to police violations after the fact. Unless this imbalance in the regulation of labeling and advertising is corrected, the committee finds it likely that aggressive promotion of tobacco-related PREPs, accompanied by incomplete and possibly inaccurate or misleading health-related claims, may well undermine other public health efforts to promote cessation of smoking and other forms of tobacco use. In short, unless the regulation of labeling and advertising of all tobacco-related products with health claims can be brought to parity, the impending availability of tobacco-related PREPs could cause more harm than good.

As a corollary, the committee concludes that the evidentiary base for regulating labeling and advertising must include not only scientific studies related to toxicology and human biology but also scientific analyses of the impact of particular claims, as well as messages and images in advertising and promotional activity, on risk perception and risk communication. Such analyses should take into account the overall public health goal of reducing tobacco-related morbidity and mortality both in individuals and in the population as a whole as well as the goal of enhancing the capacity of each adult to make an informed decision concerning the use of tobacco. The regulatory agency should have the resources and funding to conduct relevant consumer surveys and analyses as well as the authority to require such studies from manufacturers.

The committee has aimed to balance two possible types of errors: (1) allowing reduced-risk claims that turn out to be erroneous, and (2) deterring the development of modified products that would reduce exposure to known toxicants (and that would eventually be shown to reduce disease risk) if they were marketed. The committee acknowledges that manufacturers might forego the necessary investment in product development because of doubts that the accuracy of their claims can be defended successfully to unduly skeptical regulators. However, the most important considerations are unproven or premature reduced-risk claims and reduced-exposure claims that are mistakenly interpreted as reduced-risk claims. The regulatory process should not discourage or impede scientifically grounded claims of reduced exposure, as along as steps are taken to ensure that consumers are not misled into believing (in the absence of sound evidence) that smoking the modified product is (or is likely to be) less hazardous than smoking the conventional product. How the complex of claims and caveats associated with PREPs can best be articulated in labeling is one of the major challenges facing the regulatory agency. On the one hand, the public health is not well served by the continued use of poorly defined terms such as "light," "low tar," or other phrases that imply a benefit when none has been proven to exist. On

PM3006857039

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

- Only a handful of tobacco-related PREPs are currently known to be under development, suggesting a relatively low volume of new applications compared with the hundreds of applications for drugs and devices that are handled annually by FDA.
- The success at FDA of the user fee mechanism, in combination with a budgetary appropriation, in providing resources to support an adequate staff suggests a model of public–private funding for the review of claims for tobacco-related PREPs.

Principle 5: Labeling, Advertising, and Promotion

The labeling, advertising, and promotion of all tobacco-related products with exposure reduction or risk reduction claims must be carefully regulated under a "not false or misleading" standard, with the burden for proof of the claim resting on the manufacturer, not the government. The responsible agency should have the authority and resources to conduct surveys of consumer perceptions relating to these claims.

Labeling requirements and restrictions on advertising and other promotional activity are core elements of product safety regulation. In a previous report focusing on preventing initiation of tobacco use (IOM, 1994), another IOM committee recommended that warnings concerning the risks of using tobacco products be strengthened and made more salient, that advertising be restricted to a text-only format, and that many types of promotional activity be severely curtailed. These measures are still needed to reduce youth uptake, to promote cessation, and—most pertinent to this committee's charge—to ensure that public understanding of the dangers of tobacco use is not obscured or compromised by the marketing and promotion of a new generation of modified tobacco products purporting to be "safer" than conventional products. From this perspective, adequate regulatory authority to promote accurate public understanding of the health effects of tobacco-related PREPs is perhaps the single most important feature of effective regulation.

The burden of proving any claim of reduced exposure or reduced risk should rest on the manufacturer. The evidentiary base for such claims must meet contemporary scientific standards and be fully available for independent review by a responsible regulatory body. Independent review and replication of key findings—the "gold standard" for validating scientific assertions—is a compelling necessity for assessing health-related claims associated with tobacco products. Unfortunately, in today's regulatory environment for tobacco products, this proper burden of proof is reversed. Manufacturers are free to market new tobacco products with explicit or implied health claims until challenged by the FTC, which must then show in court, through expert testimony and consumer surveys, that a particular advertising claim is deceptive and not adequately substantiated. Regulation of claims through this process may take years and offers no chance for prompt correction of misleading advertising. The committee anticipates that under the current regulatory conditions, tobacco manufacturers are no more likely to present—accurately and with appropriate caveats, warnings and uncertainties— what is known, and unknown, about the potential health effects of PREPs than they have been to describe accurately the risks of conventional cigarettes.

The committee therefore strongly recommends that new legislation be enacted to ensure that the labeling, advertising, and promotion of all tobacco-related products are carefully regulated so that exposure reduction and risk reduction claims are supported by adequate scientific evidence and are not false or misleading. Claims made in the product labeling should be subject to premarket approval by the regulatory agency, as explained in connection with principle 4. Although a routine requirement for prior approval of advertising might not be constitutionally

PM3006857040

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

The committee judges that exposure reduction and risk reduction claims for tobacco-related PREPs should be treated as analogous to "effectiveness" claims for drugs and devices. Just like drug claims, they are intended to assure consumers of a potential health benefit if the product is used as directed, and just like drug claims, they should be presented accurately and supported by appropriate scientific data. As discussed in Section II of this report, the committee is not aware of a sound scientific basis at the present time for an unqualified risk reduction claim for any tobacco-related PREP. Although the potential for reduced-risk products exists, data supporting such claims have never been subject to comprehensive, independent scientific scrutiny or regulatory review. In no case has the degree of potential risk reduction been estimated from animal or human studies, nor have surveillance programs been implemented to monitor the long-term outcome of the use of any of these products. Uncertainty about the health effects of all PREPs will therefore continue for years even if an effective regulatory framework is created in the near term. If no such framework is created, consumers will continue to act on deficient information.

With respect to the tobacco-related PREPs known to the committee, the most that can reasonably be said today on the basis of the publicly available data supplied by manufacturers is that these products reduce exposure to some but not all of the toxic ingredients in cigarettes, assuming no increase in the total number of cigarettes smoked or in other forms of compensatory smoking. Direct evidence will not be available for many years, if ever, to prove that the degree of exposure reduction achieved, if maintained over years, is sufficient to result in a significant reduction in morbidity and mortality. The use of reduced-nitrosamine tobacco, for example, seems likely to reduce the exposure of smokers to nitrosamines, but whether this will reduce lung cancer rates, given the other carcinogens in tobacco smoke, is unknown (see Chapter 12). Similarly, the use of the cigarette-like product Eclipse™ may reduce exposure to carcinogens but increase exposure to CO. Whether these and similar products, if smoked chronically like cigarettes, will provide a net benefit in terms of all-cause mortality is unknown and can only be determined by long-term epidemiological studies.

Products that increase exposure to one or more tobacco toxicants while reducing exposure to others will present a complex challenge to the regulatory agency. At a minimum, approved claims of reduced exposure should be accompanied by warning statements regarding any increased exposure. Moreover, in the committee's view, reduced-risk claims should be permitted for such a product only if the agency finds, based on scientific evidence, that the use of the product can reasonably be expected to reduce the overall risks of tobacco-related disease or death. While recognizing that the proposed premarket approval requirement raises the possibility of regulatory delays and may inhibit the marketing of new tobacco-related PREPs, The committee believes that undue delay can be minimized by an efficiently administered agency for the following reasons:

- The body of scientific information submitted for review of each new product is likely to be substantially less than that in a typical new drug application to the FDA. For most such products the scientific evidence supporting exposure reduction claims will come from in vitro studies, animal studies, and pharmacokinetic studies in humans. Depending upon the claim, evidence may also come from short-term clinical studies of pulmonary function and/or cardiovascular function. The huge clinical trial programs required to show the effectiveness and safety of drugs in humans would not be necessary to support exposure reduction claims for tobacco-related PREPs.

PM3006857041

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

Principle 4: Premarket Approval of Claims

Manufacturers should be permitted to market tobacco-related products with exposure reduction or risk reduction claims only after agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that independent scientific experts would anticipate finding a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies..

Products accompanied by explicit or implicit claims of reduced exposure to tobacco toxicants or reduced risk of adverse health effects should be subject to premarket approval of the specific claim. Under this approach, manufacturers would be permitted to market products with claims of reduced exposure or reduced risk (compared with whatever benchmark product is stated in the labeling) as long as the claim is approved on the basis of appropriate scientific data by the regulatory agency before marketing and, where judged necessary for risk reduction claims, appropriate plans for post-marketing surveillance are also approved.

When the committee refers to a "reduced risk" claim in this chapter, it is referring to any statement, however qualified, indicating that use of the product presents or may present a reduced risk of disease or other adverse health effect, compared with use of some other tobacco product.

Premarket approval of tobacco-related PREPs with claims of reduced exposure or reduced risk is essential to ensure that full information is presented to potential consumers. Under the current regulatory system, manufacturers may, in the absence of drug claims, introduce new or modified tobacco products into the marketplace without any prior regulatory review, subject only to the FTC's authority to enjoin "deceptive acts and practices" after the deception has already occurred. The result has been the long history, cited elsewhere in this report, of promotional practices by tobacco manufacturers that have, at the least, obscured the adverse health consequences of tobacco use. The committee considers it highly unlikely that tobacco-related PREPs marketed under this system would be labeled and promoted with appropriate caution, especially if the market becomes competitive.

The premarket approval model used for the review of new drugs, while not now applied to new brands and modifications of conventional tobacco products marketed without disease claims, in fact provides the only fail-safe procedure for the review of exposure reduction or risk reduction claims relating to tobacco products, whether made on behalf of novel products like Eclipse™ or in connection with products already on the market (e.g., smokeless products). The committee thus recommends that any new legislation must provide for premarket approval of claims of exposure reduction or risk reduction. The medical device provisions of the FDCA provide a model for this policy in that high-risk products are subject to premarket approval, while products of lesser risk are subject only to premarket notification. The marketing of a new tobacco-related product with an unsubstantiated claim of reduced disease risk (including a claim of reduced exposure that implies a reduced disease risk) is probably a greater threat to public and personal health than the marketing of a product already known to be dangerous, unless the claim is proven to be accurate. The scientific evidence behind such a claim thus deserves full and independent scrutiny.

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

The agency might also require that tar and nicotine yields be presented in a standard format, such as absolute content together with a statement of the range of expected systemic yield determined according to number of puffs or other behavioral factors. Currently, marketed cigarettes typically *contain* 8–9 mg nicotine in the tobacco rod, and have an expected actual yield to the smoker of 0.5–3.0 mg nicotine. Stating the nicotine content of the tobacco contained in the cigarettes is important because the content reflects the maximum possible yield, and reduction of content would be expected to result in a reduction in actual yield. Manufacturers might be required to convey this information on the package or through package inserts. In order to avoid misunderstanding, the agency might require consumers to be told that small differences in nominal yield do not reflect significant differences in health risks. Regulations of this nature will improve risk perception among consumers, and will correct any misleading impression about the relative hazards of cigarettes containing different levels of tar and nicotine. From the same perspective, the agency should be authorized to ban or regulate use of misleading terms (such as "light") in advertising or on packaging, and should be authorized to require the use of standard terms.

Principle 3: Toxicity Testing

Manufacturers should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models and appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the methods and results of such testing to the regulatory agency.

Under the regulatory arrangements recommended by the committee, tobacco manufacturers would have to obtain appropriate toxicological data from the scientific literature or conduct toxicological testing in connection with any new product or modification of an existing product (1) to support a claim of reduced exposure or reduced risk (see principle 5), (2) to demonstrate that a new ingredient does not increase the product risk (see principle 7), or (3) to satisfy the requirements of the added-ingredients review described in principle 8.

Because clinical trials on the long-term health risks of individual ingredients in tobacco-related PREPs cannot reasonably be conducted in humans, any scientific assessment of the risks, except perhaps low birth weight and sudden cardiac death, of added ingredients must necessarily be based on animal studies, short-term human studies and epidemiological studies. For ingredients that have not previously been used in conventional or modified tobacco products, animal studies to support their safety should be conducted by the manufacturer prior to human exposure to those ingredients. The committee believes that the practice of introducing new ingredients into smoked products without full and adequate testing of such ingredients, as judged by a competent regulatory agency, poses a substantial risk to the consumer and should cease. A requirement for adequate preclinical testing of potentially toxic ingredients is a basic feature of all regulatory laws relating to drugs, biologics, devices, food additives, toxic chemicals, and environmental contaminants and should apply as well to conventional and modified tobacco products.

PM3006857043

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

different depths of inhalation. As a result, for any product, the temperature of combustion and the composition of the smoke varies among smokers depending on the pattern of smoking. The information required to address the relative harmfulness of tobacco products will be available only if an improved methodology for ascertaining the range of actual toxicant yields in human consumers is developed and applied; only then will there be a scientific basis for developing some of the features of a harm reduction program, including, for example, accurate labeling, meaningful definition of terms such as "low tar", and reasonable standards for yields of tar, carbon monoxide (CO), or nicotine.

Although the limitations of the FTC's current methodology for assessing cigarette yield is generally acknowledged, no definitive steps have been taken to replace it. In 1994, the President's Cancer Committee and the National Cancer Institute (NCI) issued a report criticizing the current approach and recommending adoption of a new one. In 1997, the FTC issued a proposed revision of the methodology and a proposed format for disclosing test results in advertising and labeling. However, many proponents of a new approach urged the FTC to defer action pending judicial clarification of the FDA's authority and, possible congressional enactment of comprehensive regulation for tobacco products. It is time for the FTC—or, ideally, an agency with regulatory authority over tobacco products—to adopt a new standardized methodology to assess the range of toxic exposures to smokers under actual conditions of human smoking.

Although the focus of yield assessment has been smoked tobacco, an analogous methodology should also be developed for smokeless products. Without quantitative information on the absorption of various constituents under normal product use, it is impossible to assess comparative exposures and comparative risks.

The committee embraces the conclusions and recommendation on this issue set forth in the IOM (1994) report *Growing Up Tobacco Free*:

> [T]he regulatory agency, as its first step, should develop a sound methodology for ascertaining the actual yields of nicotine, tar, or any other constituents of tobacco products, based on human consumption. Human exposure to some constituents of tobacco smoke can be assessed by use of biochemical markers of exposure to those constituents, although at present this methodology is technically difficult and still imprecise; however, it is likely that better exposure measures will be developed in the future. In any case, even the currently available measures of human exposure are likely to provide a better indicator of relative risk than do the standard cigarette smoking machine yields. At a minimum, the smoking machine tests can be modified to reflect the range of ways in which people actually smoke, including numbers of puffs and blocking of ventilation holes, to determine likely *ranges* of delivery. In addition, the manufacturers of tobacco products could be directed to submit information to the regulatory agency regarding the actual yields of their products in humans for particular brands of tobacco products, based on use of prescribed protocols.
>
> A variety of regulatory initiatives relating to tar and nicotine yields can be envisioned. At a minimum, the regulatory agency should take steps to assure that consumers are informed about the meaning of statements regarding tar and nicotine yields, about the behavioral influences on exposure, and about the relative importance of the characteristics of the cigarette and the way it is smoked.

PM3006857044

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

Principle 1: Disclosure of Product Ingredients

Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency.

The manufacturers of tobacco products have detailed and extensive knowledge of the composition, curing, and blending of tobacco; the ingredients of their products; and the composition of tobacco smoke. They also have detailed quantitative information on the tobacco in each of their brands of cigarettes and smokeless products, since each is blended to achieve the desired taste and levels of nicotine and other ingredients. Manufacturers also conduct major R&D programs aimed at developing new products. Currently, there is no requirement for disclosure of this information to an appropriate regulatory body. Such disclosure is prerequisite to any meaningful scientific appraisal of the comparative risks of different tobacco-containing products or the potential for risk reduction offered by modified products. For smoked products, analytical information on the smoke and the concentrations of smoke components that are absorbed under actual smoking conditions may be even more important than knowledge of the product ingredients themselves. For smokeless tobacco products, whether conventional or modified, similar information on the concentrations of major ingredients in saliva and blood are equally important. The disclosure of quantitative information on ingredients (with appropriate safeguards to protect trade secrets) is a standard requirement in regulatory laws relating to drugs, biologics, devices, food additives, toxic chemicals, and environmental contaminants and should be required of all tobacco products, whether conventional or modified.

Although FTC regulation requires public reporting of some constituents in cigarette smoke, manufacturers are not required to report brand-specific information about the nicotine content or other properties (e.g., nitrosamine level) of the material that forms the tobacco rod. Under legislation enacted in 1986, manufacturers of smokeless products are required to report total nicotine content to the secretary of the Department of Health and Human Services (HHS), but the secretary may not release the data. Under the same legislation, tobacco manufacturers are required to submit lists of additives to the tobacco (but not to filters or papers) to the secretary of HHS. Information about the quantity of additives and their presence in specific brands is not required, and the secretary is bound to safeguard the information from public disclosure. In 1993, attorneys for six cigarette manufacturers released a combined list of 599 additives. The following year, ten manufacturers of smokeless products released a list of additives in their products. Three states have enacted legislation requiring disclosure of additives in tobacco products (U.S. DHHS, 2000).

Principle 2: Yield Assessment

All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects real parameters of human consumption; when necessary to support claims, human exposure to various constituents of tobacco smoke should be assessed using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading.

The actual yield—that is, the amount of toxicants inhaled by an individual—from particular cigarettes varies considerably among smokers. As discussed in Chapter 11, this is because the standard yield is measured by a machine that smokes cigarettes in a mechanical and standardized way, whereas smokers can and do smoke their cigarettes with different numbers of puffs and

PM3006857045

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

using appropriate biomarkers. Accurate information regarding yield range and human exposure should be communicated to consumers in terms that are understandable and not misleading.

3. Manufacturers of all PREPs should be required to conduct appropriate toxicological testing in preclinical laboratory and animal models and appropriate clinical testing in humans to support the health-related claims associated with each product and to disclose the results of such testing to the regulatory agency.

4. Manufacturers should be permitted to market tobacco-related products with exposure reduction or risk reduction claims only after agency approval based on scientific evidence (a) that the product substantially reduces exposure to one or more tobacco toxicants and (b) if a risk reduction claim is made, that the product can reasonably be expected to reduce the risk of one or more specific diseases or other adverse health effects, compared with whatever benchmark product the agency requires to be stated in the labeling. The "substantial reduction" in exposure should be sufficiently large that independent scientific experts would anticipate finding a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies.

5. The labeling, advertising, and promotion of all tobacco-related products with exposure reduction or risk reduction claims must be carefully regulated under a "not false or misleading" standard, with the burden of proof for the claim resting on the manufacturer not the government. The responsible agency should have the authority and resources to conduct surveys of consumer perceptions relating to these claims.

6. The regulatory agency should be empowered to require manufacturers of all products marketed with claims of reduced risk of tobacco-related disease to conduct postmarketing surveillance and epidemiological studies as necessary to determine the short-term behavioral and long-term health consequences of using their products and to permit continuing review of the accuracy of their claims.

7. In the absence of a claim of reduced exposure or reduced risk, manufacturers of tobacco products should be permitted to market new products or modify existing products without prior approval of the regulatory agency after informing the agency of the composition of the product and certifying that the product could not reasonably be expected to increase the risk of cancer, heart disease, pulmonary disease, adverse reproductive effects, or other adverse health effects, compared to similar conventional tobacco products, as judged on the basis of the most current toxicological and epidemiological information.

8. All added ingredients in tobacco products, including those already on the market, should be reported to the agency and be subject to a comprehensive toxicological review.

9. The regulatory agency should be empowered to set performance standards (e.g., maximum levels of toxicants; definitions of terms such as "low tar") for all tobacco products, whether conventional or modified, or for classes of products.

10. The regulatory agency should have enforcement powers commensurate with its mission, including the power to issue subpoenas.

11. Exposure reduction claims for drugs and devices that are supported by appropriate scientific and clinical evidence should be allowed by the FDA.

The following sections elaborate on each of these principles.

PM3006857046

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

which risk-reduction claims are made would be subject to postmarketing epidemiological studies.

- New brands and modifications of conventional tobacco products without health claims would be permitted to enter the market without prior regulatory approval if they are certified to present "no greater risk" than products already on the market.
- Pharmaceutical products and medical devices, whether nicotine containing or not, with health claims for reduction of smoking would continue to be subject to the current requirements of the FDCA.

The committee believes that the agency charged with regulating tobacco PREPs should have a public health orientation and should be given authority over all tobacco products, including conventional ones. The scientific expertise needed to regulate both categories of products is similar. This agency will require a competent scientific review staff, including molecular biologists, pharmacologists, toxicologists, physicians, epidemiologists, statisticians, and scientists experienced in the technology of tobacco product design and manufacture. In addition, it will need social scientists and marketing experts experienced in the evaluation of product labeling and the regulation of advertising. The agency must also have an analytical laboratory capable of testing a wide range of conventional and modified tobacco products and a product surveillance program staffed with epidemiologists and data management experts. Finally, it will need an enforcement and legal staff and appropriate administrative and information technology personnel.

Some of these functions already exist for tobacco products at the Food and Drug Administration (disease claims), at the Federal Trade Commission (FTC; regulation of advertising and enforcement staff), and at the Centers for Disease Control and Prevention (CDC; analytical laboratory). But no agency currently has the comprehensive mandate or staff necessary to fulfill the policies recommended by the committee. This committee, like previous IOM committees (IOM, 1994, 1998), believes that the FDA would be an appropriate site for this regulatory function, but other administrative locations are certainly possible. The important point is that the requisite authority be lodged in a suitable federal regulatory agency with sufficient expertise and resources to execute the mission successfully.

The committee notes the efforts of some states, notably Massachusetts in particular, to take on some of the regulatory challenges created by the federal government's failure to establish comprehensive regulatory authority over tobacco products. However, patchwork state legislation is not a satisfactory long-term response to the problem. The only adequate response is for Congress to confer comprehensive authority on a suitable federal agency.

Summary of Regulatory Principles

A science-based regulatory framework for implementing tobacco harm reduction should conform to the following 11 principles:

1. Manufacturers of tobacco products, whether conventional or modified, should be required to obtain quantitative analytical data on the ingredients of each of their products and to disclose such information to the regulatory agency.
2. All tobacco products should be assessed for yields of nicotine and other tobacco toxicants according to a method that reflects actual circumstances of human consumption; when necessary to support claims, human exposure to various constituents of tobacco smoke should be assessed

PM3006857047

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

1. conventional tobacco products and modified products that are marketed without claims of reduced exposure to tobacco toxicants or reduced risk of disease;
2. modified tobacco products or tobacco-like products, whether tobacco containing or not, that are marketed with such claims; and
3. pharmaceutical products and medical devices, whether nicotine containing or not, that are marketed with a claim of effectiveness for cessation of, or significant reduction in, smoking.

The committee's charge is directed to products in categories 2 and 3 (all PREPs). The legal structure for regulating pharmaceuticals in category 3 is already fully in place under the federal Food, Drug and Cosmetic Act (FDCA) and administered by the FDA. The committee has therefore largely focused on products in category 2, a classification that encompasses any tobacco-related product marketed as a PREP—that is, with claims of reduced exposure to tobacco toxicants or reduced risk of disease—presumably involving a novel design or a modification of a conventional tobacco product. In the interest of placing recommendations concerning the regulation of tobacco-related PREPs in the larger regulatory context, the committee has embraced several recommendations in previous reports of the IOM (1994, 1998) with respect to conventional tobacco products (category 1 above). Thus, several of the principles outlined below apply to conventional tobacco products as well as to tobacco-related PREPs.

Taken together with the drug and device laws already in place, the overall regulatory system should be sufficiently broad and flexible to encompass all relevant product innovations and to respond to new scientific knowledge in the years ahead. Manufacturers of tobacco products and pharmaceuticals should be encouraged to develop and introduce new products that will reduce the burden of tobacco-related disease. However, manufacturers of new products should not be allowed to escape regulatory oversight by claiming that their products are dietary supplements, herbals, botanicals, or foods or that they make no explicit claims.

PRINCIPLES FOR REGULATING POTENTIAL REDUCED-EXPOSURE PRODUCTS

In the remainder of this chapter, the committee offers its judgment for consideration of the challenging scientific issues presented by the complex array of new products offered with claims bearing on tobacco harm reduction. Specifically, the committee proposes 11 principles that it believes should govern the regulation of new or modified tobacco products and pharmaceutical products with harm-reducing potential. The overall regulatory structure builds on the foundation of existing regulatory law, with appropriate adaptations to take into account the unique history and toxicity of tobacco products. The committee's approach reflects the following general configuration:

- All tobacco products would be subject to requirements for certain testing and reporting and to the regulation of labeling and advertising.
- A manufacturer who wishes to market a new tobacco product as a PREP—a product with a claim, whether explicit or implicit, of reduced exposure to one or more tobacco toxicants or of reduced risk of adverse health effects (compared with conventional products)—would be required to receive from the regulatory agency prior approval of the claim based on scientific evidence presented by the manufacturer that the claim is not false or misleading; products for

PM3006857048

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

- a well-designed program of public health *education* (including media campaigns) to help people understand that preventing the initiation of smoking and assisting smokers to quit constitute the only proven methods of minimizing tobacco-related harm, that the health benefit of using PREPs remains uncertain, and that this uncertainty will not be resolved for many years; and
- An integrated program of federal *regulation* of both tobacco-related PREPs and pharmaceutical PREPs designed to protect public health and to facilitate the research, surveillance, and public education activities described above.

The remainder of this chapter will set forth the committee's recommendations regarding the regulation of PREPs. As discussed in Chapter 4, the current regulatory situation leaves conventional tobacco products essentially unregulated while imposing stringent regulatory controls on the development and marketing of pharmaceutical PREPs. Modified tobacco products with exposure-reduction claims currently fall into a twilight zone of regulatory uncertainty.

Previous reports of the Institute of Medicine (IOM, 1994,1998) have recommended that Congress enact a comprehensive regulatory statute delegating to an appropriate agency, preferably the Food and Drug Administration (FDA), "the necessary authority to regulate tobacco products for the dual purpose of discouraging consumption and reducing the morbidity and mortality associated with use of tobacco products." The need for comprehensive tobacco regulation, as recommended in these previous reports, is reinforced by the Supreme Court's ruling, on March 21, 2000, that the FDA lacks comprehensive authority over tobacco products under the Federal Food, Drug and Cosmetic Act (LII, 2000). These reports also recommended that the designated agency be authorized to regulate the design and constituents of tobacco products—for example, by adopting "performance standards" that set limits for the levels of toxicants in all tobacco products and/or by regulating the levels of, or exposure to, nicotine. This committee endorses these recommendations.

This committee's charge focuses specifically on products that purport to reduce exposure to tobacco toxicants. In this context the need for federal regulation is made more urgent by the recent introduction of Advance™ and the expansion of Eclipse™ into the marketplace and by the likely introduction of other tobacco-related PREPs, including oral nicotine and Swedish snus, in the future. The FDA already has the authority to regulate certain of these new or modified tobacco products as drug-delivery devices or as "drugs" if the manufacturer claims that the product prevents disease by reducing the health risks of using tobacco. The scope of the FDA's jurisdiction is unclear, though, if the manufacturer goes no further than claiming that the product reduces exposure to known tobacco toxicants (Page, 1998). Whatever the reach of FDA's current jurisdiction over modified tobacco products, the existing regulatory framework for all tobacco products, including tobacco-related PREPs is inadequate to provide a basis for informed consumer choice and to protect the public health. Accordingly, **the committee recommends that Congress enact legislation enabling a suitable agency to regulate tobacco-related products that purport to reduce exposure to one or more tobacco toxicants or to reduce risk of disease, and to implement other policies designed to reduce the harm from tobacco use.**

Regulatory classifications are traditionally based on the use(s) of a product and/or the claims associated with it. The outline of a sensible regulatory classification is therefore as follows:

PM3006857049

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

evidence. Action should therefore be taken not only to monitor the market, but also to shape it as scientific knowledge unfolds. Despite continuing ambivalence among some health officials about the wisdom of embracing harm reduction as a public health policy, numerous consumers will be taking steps in this direction, with or without scientific guidance. The aggregate effect of these decisions might make an important contribution to public health—or might further exacerbate the problems posed by tobacco products. Policy makers must use the best that science has to offer to ensure that the harm reduction strategies pursued by tobacco and pharmaceutical manufacturers and by individual consumers will truly reduce harm, and to the greatest extent possible.

The committee was drawn by its charge into considering how best to implement the scientific and policy recommendations in this report and, in so doing, was necessarily required to address some features of a regulatory framework for PREPs. The regulation of tobacco products is most certainly controversial and many approaches have been proposed. Tobacco regulation conceivably includes taxation, access by minors, point of sales, etc. For the purposes of this report the regulatory framework considered is narrow and focused exclusively on evidence and any necessary powers required to assess harm reduction products, be they pharmaceutical or tobacco-related. Other aspects of possible tobacco regulation are outside of the charge of this committee.

The committee did come to conclude that regulation of PREPs is necessary and feasible. First, effective regulation is a necessary precondition for advancing scientific knowledge on the toxicology and clinical effects of these products, for developing the data necessary for systematic risk assessment, and for monitoring the impact of such products on the public health through appropriate postmarketing surveillance and the collection of long-term epidemiological data. Second, regulation is needed to ensure that the product labeling and advertising do not mislead consumers and accurately describe the products' risks, including the uncertainties that can only be resolved after long-term use. Consumers should not use these new products on the basis of explicit or implicit claims that these products carry less risk than traditional tobacco products unless such claims are true. Absent careful regulation of industry claims about these products, informed choices by consumers will not be possible, the potential benefit of a harm reduction strategy is likely to go unrealized, and the long and unsettling saga of light cigarettes may well be repeated. Finally, regulation is also needed to foster integrated, coherent, and equitable policies with respect to the scientific testing, labeling and advertising of the diverse array of PREPs marketed by tobacco and pharmaceutical companies.

NEXT STEPS: AN OVERVIEW

Although the science base for tobacco harm reduction (summarized in Chapter 5 and described in detail in Chapters 9–16) is extensive, the committee identified many gaps and limitations. To improve the science base for a harm reduction strategy for tobacco products and to protect public health, the committee's scientific findings and conclusions must be translated into a comprehensive policy framework that includes the following elements:

- a substantial and sustained *research* program to address the critical unresolved questions that are susceptible to scientific resolution, as identified in this report;
- a strong *surveillance* program that will serve both as an "early warning system" for identifying problems associated with PREPs and as an epidemiological tool for evaluating long-term health consequences;

PM3006857050

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001

7

Implementation of a Science-Based Policy of Harm Reduction

Scientific evidence establishes unequivocally that tobacco use causes serious adverse health effects in humans and that the nicotine delivered by tobacco is a highly addictive drug. The ultimate public health goal of tobacco policy is to eliminate the excess morbidity and mortality associated with tobacco use. The only scientifically proven way to accomplish this is to eliminate tobacco use by preventing initiation by those who have never used tobacco, achieving cessation for those who currently use tobacco, and preventing relapse by former users of tobacco. Achieving this goal will protect tobacco users themselves and those affected by environmental tobacco smoke (ETS). But because nicotine is a highly addictive drug, quitting tobacco use is extremely difficult for many people. Despite overwhelming evidence and widespread recognition that tobacco use poses a serious risk to health, some tobacco users cannot or will not quit. For those addicted tobacco users who do not quit, reducing the health risks of tobacco products themselves may be a sensible response. This is why many public health leaders believe that what has come to be called "harm reduction" must be included as a subsidiary component of a comprehensive public health policy toward tobacco.

Some public health officials oppose the adoption of harm reduction strategies because of concerns that promoting this approach will not, over the long term, prove to be beneficial to public health or to the individual tobacco users who might otherwise have quit (Ferrence et al., 2000; Warner et al., 1997). Whatever the merits of this position, marketplace forces already at work have put this issue on the public policy agenda, and new products are being developed and offered as harm-reducing alternatives to conventional tobacco products. The task before this committee is to address the science base for implementing a harm reduction approach, and for assessing the impact of such an approach on public health. The committee's task is not to recommend whether or not tobacco harm reduction should be pursued. Furthermore, the committee's effort to carry out its charge should be understood as only one component of a comprehensive tobacco control policy.

This report shows that the prospect of harm reduction presents both promise and uncertainty. For tobacco and pharmaceutical companies to be investing in products that reduce exposure to tobacco toxicants could be a salutary development. Nonetheless, despite advances in understanding tobacco toxicology and the pathophysiology and epidemiology of tobacco-related diseases, little is known about the health effects of using products that reduce exposure to one or more tobacco toxicants or about the public health consequences of promoting tobacco-related products or pharmaceutical products as potential reduced-exposure products (PREPs). It will take many years of research to develop definitive data. It is also clear, however, that action must be taken now, even as better data are being developed, to respond to the already emerging market for PREPs and to ensure that the necessary data are developed, that consumers are accurately informed, and that the public health is fostered.

Until adequate data are available, individual and regulatory choices will by necessity have to be made on the basis of predictions of risk and harm reduction based on inference from indirect

PM3006857051

Source: https://www.industrydocuments.ucsf.edu/docs/fylx0001